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Methotrexate for the Treatment of Unruptured Tubal Pregnancy: A Prospective Nonrandomized Study

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ABSTRACT

Background and Objectives: The aim of this study was to compare in a prospective nonrandomized study, the efficacy of 2 methods of administering methotrexate (MTX) in the treatment of ectopic pregnancy (EP): transvaginal injection under sonographic control or intramuscular injection (IM).

Methods: Patients with EP who met specific inclusion criteria for medical treatment were treated with MTX: 63 patients (group 1) were treated by IM and 47 patients (group 2) by transvaginal local injection. In group 1, 50 mg/m^2 of MTX was injected intramuscularly; in group 2, transvaginal injection of 1 mg/kg of MTX was injected into the ectopic sac under sonographic control. When an additional dose of MTX was required, it was administrated IM at the dosage of 50 mg/m^2 in both groups.

Results: The overall success rate, defined by a posttreatment normal hCG level (<10 mUI/mL) was 71.4% in group 1 versus 91.5% in group 2 (P<0.01); for patients with hCG levels <2000 mUI/mL, 83% and 96%, respectively (not significant); for patients with hCG ≥2000 mUI/mL, 37.5% and 86.4%, respectively (P<0.01).

Conclusion: In the medical treatment of EP, the efficacy of MTX is greater when administered by local transvaginal injection than by IM injection. We propose local treatment every time EP can be punctured, especially when hCG levels are ≥2000 mUI/mL.

Key Words: Ectopic pregnancy, Local methotrexate, IM methotrexate.

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INTRODUCTION

Early diagnosis of ectopic pregnancy (EP) has been made possible by a variety of factors including information regarding its risk factors (ie, history of pelvic inflammatory disease, tubal surgery or ectopic pregnancy, smoking habits, use of infertility drugs, contraception failure), the development of radioimmunoassays, and specific antiserum to the b-subunit of hCG that provide sensitive and specific detection, the use of serum progesterone, and high resolution sonography with vaginal probes. When EP is discovered early, laparoscopy can frequently be avoided, and a nonsurgical approach proposed.

Since the first publication by Tanaka et al,[1] many series have reported the results of conservative medical treatment with methotrexate (MTX) in EP. They have used IM or IV injection of 1 to 4 doses,[1-6] oral,[7] or local injection under laparoscopic[8-10] or sonographic control.[11-15] We have previously reported MTX failure rates similar to those reported in conservative laparoscopic surgery when appropriate inclusion criteria are used.[13] More recently, prospective randomized studies by Hajenius et al,[16] Fernandez et al,[17] and Saraj et al,[18] comparing laparoscopic salpingotomy and MTX treatment, reported that the 2 treatments have similar success rates and similar subsequent fertility.

However, substantial differences exist in the various sets of results, and the success rates range from 61%[15] to 93%[16] for the local treatment and from 65%[19,20] or 78%[21] to 94%[5] for the IM treatment. These discrepancies suggest that selection criteria have varied from study to study. Our continuing experience with methotrexate has shown that the modality of administration, in particular whether injection is IM or local transvaginal under sonographic control, affects success rates. No published series compare IM injections with the local route. We conducted this prospective, nonrandomized study in a series of 110 patients with EP, all selected according to the same criteria.

MATERIALS AND METHODS

The study was performed between September 1, 1992

and November 30, 1997. The local institutional review board approved the nonsurgical approach for treating EP. Criteria were an unruptured ectopic pregnancy in whom hematosalpinx was directly visualized by pelvic ultrasound, a pretherapeutic score less than 13 (this score is based on 6 criteria graded on a scale from 1 to 3: gestational age, hCG level, progesterone level, pelvic pain, hemoperitoneum volume, and hematosalpinx diameter[22]), and a second blood test at 48 hours showing a stable or progressing level of hCG.

During the study period, 418 EP were diagnosed overall; 286 (68.9%) underwent surgical treatment immediately after diagnosis. Nonsurgical methods were used in 132 (31.9%) patients: 12 with expectant management when hCG levels were decreasing at 48 hours, 10 by MTX treatment IM for whom hematosalpinx was not directly visualized by pelvic ultrasound, and 110 patients were included in the study with MTX management. In this group, MTX administration was either IM (group 1, n=63) or injected directly into the hematosalpinx (group 2, n=47). In group 1, the dosage of MTX IM was 50 mg/m2 as suggested in the protocol of Stovall et al.[4] In group 2, MTX was injected locally without anesthesia, under sonographic control, with an 18-gauge needle inserted into a needle introducer. Penetration and aspiration of the ectopic sac were followed by an injection of 1 mg/kg of MTX into the hematosalpinx. The dosage of 1 mg/kg locally was determined by a previously reported pharmacokinetic study.[23]

Two groups of physicians with differing amounts of experience with medical treatment participated in this study: 1 group had good experience with transvaginal puncture and usually administrated a local treatment; the other group did not and always chose the IM route. The same experienced physician always assumed the follow-up of all medically treated patients. All patients were monitored on an outpatient basis unless they lived too far from the hospital or when the puncture was performed after 4 pm. Patients underwent hCG assays (RIA gnost-hCG, Behring, Marburg, Germany) on days 2, 5, and 8 after the injection and then weekly until normalization (<10 mIU/mL). Treatment success was defined as complete elimination of the tubal pregnancy (serum hCG <10 mIU/mL). All patients were aware of the possibility of treatment failure. An additional MTX dose of 50 mg/m^2 IM in both groups was required when hCG levels did not decline according to the reference curve:[13] rising hCG levels >140% of the initial level on days 2 or 5, hCG levels >100% of the initial level on day 8, no decrease at subsequent controls. Side effects were recorded for all patients.

To avoid an iatrogenic tubal rupture,[24,25] we avoided systematic repetition of the vaginal scan and the pelvic examination.

Characteristics and risk factors of EP were assessed for each patient: age, parity, gravidity, history of pelvic inflammatory disease, tubal surgery, or ectopic pregnancy, smoking habits, use of infertility drugs, pregnancy resulting from contraception failure, presence of cardiac activity in the ectopic sac diagnosed by transvaginal ultrasonography.

We calculated success rates after primary treatment plus any additional dose of MTX required. Failure was defined by the need for surgery.

Patients' characteristics are expressed as the mean ± SD. Indicators in the 2 groups were compared with the Student *t* test and the χ^2 test modified by Yates when appropriate.

RESULTS

Baseline demographics and characteristics are summarized in **Table 1**. Slightly more patients in group 1 (IM treatment) had a past history of pelvic inflammatory disease, and more patients in group 2 (local treatment) had a history of tubal surgery and fertility treatments.

Table 2 reports the characteristics of the tubal pregnancies and the success rates in both groups. In 7 cases, cardiac activity was detected in a sac located in the cornua. Gestational age and hematosalpinx size were the same in both groups. Both the pretherapeutic score and progesterone level were slightly higher in the local treatment group, and the pretreatment hCG level was significantly higher ($P<0.05$). The overall success rate for MTX treatment was 88 of 110 patients (80%). The success rate in the IM group was 45 of 63 (71.4%). The single-dose success rate was 41 of 63 (65.1%) patients. Twelve of 63 patients (19%) received a second MTX injection. Treatment was successful for 4 of the 12 patients who required a second MTX injection, but the other 8 (66.6%) underwent surgery. Ten patients underwent surgery after the first injection. The success rate in the local treatment group was 43 of 47 patients (91.5%). The single-dose success rate was 39 of 47 (83%). Five of 47 (10.6%)

Table 1.
Demographic and Obstetric Characteristics of 120 Patients With EP

	Intramuscular Methotrexate (n=73)	Local Methotrexate (n=47)	*P* Value*
Age	31.1±5.2 (20-43)	30.6±5.7 (20-43)	NS
Parity	0.7±0.9 (0-3)	0.6±0.9 (0-3)	NS
Gravidity	2.4±1.3 (1-7)	2.2±1.4 (1-6)	NS
Smoking	23 (31.5%)	11 (23.4%)	NS
Appendectomy	25 (34.2%)	18 (38.3%)	NS
Past history of EP	9 (12.3%)	8 (17%)	NS
Past history of tubal surgery	6 (8.2%)	9 (19.1%)	NS
Past history of PID	10 (13.7%)	4 (8.5%)	NS
Induction of ovulation	8 (11%)	10 (21.3%)	NS
Contraception failure	9 (12.3%)	3 (6.4%)	NS

*NS = Not significant.

Table 2.
Clinical, Laboratory, and Sonographic Findings in EPs. Success Rates, Number of Doses Required, and Resolution Time

	Intramuscular Methotrexate (n=73)	Local Methotrexate (n=47)	*P* Value*
Gestational age (days)	48±11.4 (35-105)	47.6±9.1 (35-70)	NS
Score	9.9±1.5 (6-12)	10.3±1.5 (7-12)	NS
Pretherapeutic hCG (mIU/mL)†	1490±2202 (116-15800)	3420±5037 (100-22600)	$P<0.05$
Pretherapeutic Progesterone (ng/mL)‡	6.1±5.1 (0.2-28.8)	8.6±8.7 (0.45-38.6)	NS
Hematosalpinx (mm)	21±8.6 (6-43)	21.3±11 (6-52)	NS
Patients requiring additional dose of MTX	13 (17.8%)	5 (10.6%)	NS
Resolution time§	24±17	29.2±11.8	$P<0.05$
Success (return to hCG<10 mUI/mL)†	54 (74%)	43 (91.5%)	$P<0.01$

*NS=Not significant.
†hCG conversion factor to SI unit=1.00.
‡Progesterone level conversion factor to SI unit=3.18.
§Failure excluded.

patients received a second MTX injection. Medical treatment was successful for 4 of the 5 patients who required a second MTX injection. Three patients underwent surgery after the first injection. The difference in these success rates for IM treatment and local treatment was statistically significant ($P<0.01$). Resolution time was significantly longer in the local treatment group ($P<0.05$).

In all, medical treatment failed in 22 cases: 18 in the IM treatment group and 4 in the local treatment group. The mean initial score was 10.5±1.4 for cases with treatment failure, and for successfully treated cases, 10.1±1.4. Laparoscopic treatment was used for 20 of the 22 patients for whom MTX failed. The remaining 2 patients underwent laparotomy in another hospital, by a surgeon inexperienced with endoscopy. In all, 3 of 22 (13.6%) patients had surgery elsewhere.

The indications for secondary surgical treatment were abdominal pain on the third day after MTX injection (n=2); increasing or stable hCG levels (n=5); moderate hemoperitoneum (≤250 cc) or tuboabdominal abortion (n=11), or both of these; tubal fissure (n=3); or rupture (n=1). Only in the latter case did an important hemoperitoneum occur (>1000 mL). Fifteen of 22 (68.2%) patients underwent conservative treatment. The 7 remaining patients underwent salpingectomy: tubal fissure or rupture (n=4), unsuccessful conservative treatment (n=2), and hydrosalpinx (n=1).

In the IM group, the mean pretreatment hCG was 1378±2609 mIU/mL for successes and 1936±1501 mIU/mL for failures. In the local group, these values were 3404±5243 mIU/mL and 3580±2015 mIU/mL, respectively. The mean pretreatment progesterone level in the IM group was 5.9±5.4 ng/mL for successes and 6.5±4.9 ng/mL for failures. In the local treatment group, these values were 7.8±7.6 ng/mL and 16.9±15.6 ng/mL, respectively. In the IM group, the mean size of hematosalpinx before treatment was 21±8.9 mm for successes and 20.8±8 mm for failures, and in the local group 22.2±11.1 mm and 12±5 mm, respectively. No cutoff values predicting failure were found in each group for hCG or progesterone levels or hematosalpinx size. When pretreatment hCG levels were <2000 mIU/mL, the success rate was 39 of 47 (83%) in the IM group and 24 of 25 (96%) in the local treatment group. When pretreatment hCG levels were ≥2000 mIU/mL, the success rate was 6 of 16 in the IM group (37.5%) and 19 of 22 (86.4%) in the local treatment group (P<0.01).

Success rates according to pretreatment score are reported in Table 3. Local injection was effective more often than IM treatment for the same initial score. Although the differences were not statistically significant, among patients with an active EP and a pretherapeutic score of 12, medical treatment was successful for 5 of 10 (50%) women in the IM group compared with 12 of 13 (92.3%) in the local group. For a score <10, treatment was successful for 16 of 20 (80%) women in the IM group and all the women (12/12) in the local group.

No clinical or biological side effects were reported for either group.

DISCUSSION

To our knowledge, this is the first study to compare the efficacy of methotrexate IM injection to the local route for medical management of EP. Methotrexate has been widely used in the nonsurgical treatment of unruptured EP and has proved its efficacy in this indication. The great heterogenicity in the published series may be attributed to the variety of protocols for MTX administration: systemic IM or IV injection,[1-6] oral administration,[7] or local injection directly into the gestational sac under laparoscopic,[8-10] or transvaginal ultrasound guidance.[11,13-15] Except in cases of interstitial pregnancy, we consider that injecting MTX under laparoscopic control tends to vitiate the main advantages of medical treatment: It is minimally invasive; and in particular, it does not require general anesthesia. A further explanation of the discrepancies among studies lies in their different inclusion criteria. Our patients were all selected with the same inclusion criteria, with the pretherapeutic score described by Fernandez et al.[22] Patients with a score <13 were treated with MTX, and only if hCG levels were stable or progressing at 48 hours. Although this study was nonrandomized, the 2 groups were comparable for demographic data and risk factors for EP. Gestational age

Table 3.
Success Rates According to Pretherapeutic Score and Cardiac Activity

	Intramuscular Methotrexate	Local Methotrexate	*P* Value*
Score = 12	5/10 (50%)	12/13 (92.3%)	NS
Score = 11	13/19 (68.4%)	8/9 (88.9%)	NS
Score =10	14/17 (82.4%)	11/13 (84.6%)	NS
Score <10	22/27 (81.5%)	12/12 (100%)	NS
Cardiac activity detected in the EP	0/1	3/4	NS

*NS=Not significant.

and hematosalpinx size were the same in both groups; the pretherapeutic score and progesterone level were slightly higher in the local treatment group, and the pretreatment hCG level was significantly higher in the local treatment group ($P<0.05$). Despite these data, the success rate with MTX was 45 of 63 (71.4%) patients with IM treatment and 43 of 47 (91.5%) patients when it was given locally ($P<0.01$), thereby confirming the superior efficacy of local administration of MTX. Its higher pretreatment hCG levels explain the longer resolution time in the local group.

Methotrexate is an antimetabolite that interferes with DNA synthesis by inhibiting the action of dihydrofolate reductase. It interrupts the synthesis of the purine nucleotide thymidylate. A previous pharmacokinetic study[23] demonstrated that when MTX was injected locally, the serum concentration changes determined an area under the curve that was lower than that when MTX was given IM. These findings may reflect decreased bioavailability of MTX captured directly by target trophoblastic cells, thereby leading to high tissue concentrations and better efficacy.

Our results are very different from those of Lipscomb et al[6] who reported a 90.1% success rate in a series of 315 patients with EP treated with MTX IM at the dosage of 50 mg/m^2. In this series, fewer than 70% of the ectopic pregnancies have been visualized by pelvic ultrasound. Our results are also quite different of those of Glock et al[26] who reported an 85.7% success rate in a series of 35 patients. Our results with IM treatment are closer to those of Stika et al[21] who reported a success rate of 78% in a retrospective study of 50 patients. The results we obtained with IM treatment may be explained by the selection of patients for whom hCG levels were stable or progressing at 48 hours and for whom hematosalpinx was directly visualized. A previous study showed a 100% specificity in the diagnosis of EP by pelvic ultrasound,[17] because all patients randomized to the salpingotomy group had hematosalpinx at laparoscopy. Our experience is probably realistic and reproducible, because it was the fruit of work by a university hospital team with not fewer than 10 physicians deciding whether a need existed for secondary urgent surgery, leading sometimes to unnecessary operations. In all the other cases, the same experienced physician always assumed follow-up. Our protocol, therefore, prevented any bias in subsequent management that might otherwise be thought to explain the important difference between intramuscular and local treatment results.

Contrary to frequent statements,[5,8,10] we found no cutoff value for pretreatment hCG and progesterone levels or hematosalpinx size. Taken one by one, none of these results accurately predicted MTX failure. This study confirms that the pretherapeutic score selects patients with EP who will be successfully treated with a local MTX injection in more than 90% of the cases.

We found that for any given pretreatment score, results were better in the local treatment group. When the score was 12, only 5 of 10 (50%) attempts with IM treatment were successful compared with 12 of 13 (92.3%) with a local treatment. When hCG pretreatment levels were <2000 mIU/mL, the success rate between IM and local treatment was not significantly different: 39 of 47 (83%) and 24 of 25 (96%), respectively. When pretreatment hCG levels were ≥2000 mIU/mL, the success rate was 6 of 16 in the IM group (37.5%) and 19 of 22 (86.4%) in the local group ($P<0.01$), confirming that local treatment should always be considered for the treatment of an active EP. In another study, Lipscomb et al[27] reported that among women with tubal ectopic pregnancies, a high serum hCG concentration was the most important factor associated with failure of treatment (but transvaginal ultrasonography revealed an ectopic mass in only 77 percent).

The results of medical treatment, when pelvic ultrasound reveals cardiac activity in the sac, were disappointing. It should be proposed rarely, when surgery might be particularly difficult, such as for patients with a cornual EP or with important bowel adhesions. All patients with a score <10 were successfully treated with local MTX, but only 16 of 20 (80%) IM treatments were successful. We conclude that justification exists for the puncture of all EPs suitable for medical treatment, even for those of low activity.

As with all new techniques, physicians need training to perform transvaginal MTX injection under sonographic guidance; with it, they improve rapidly. In this case, no specific tools are needed, and the procedure is as simple as puncturing an ovarian cyst or a follicle. Though it takes more time and is substantially more difficult than a simple intramuscular injection, our results suggest that it is worthwhile to puncture ectopic pregnancies with a score <13 every time the hematosalpinx has been visualized by pelvic ultrasound and that procedure seems safe. If hematosalpinx has not been detected or is not accessible to puncture, methotrexate IM remains the best

choice when a nonsurgical approach is possible.

Obviously, the lack of randomization reduces the value of the comparison. Results should be confirmed in a prospective, randomized trial.

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